ORGANIC
LETTERS

2011
Vol. 13, No. 2
252−255

An Extremely Active and General Catalyst for Suzuki Coupling Reaction of Unreactive Aryl Chlorides

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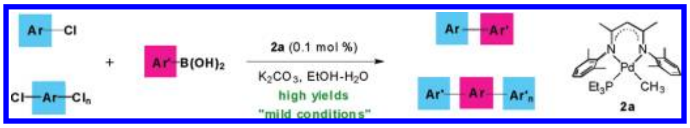
Received November 4, 2010

ABSTRACT



***β*-Diketiminatophosphane Pd complex 2a acted as a powerful catalyst which allows easy access to the Suzuki coupling reaction of less reactive aryl chlorides under mild conditions. A wide range of sterically hindered and deactivated aryl chlorides could be efficiently coupled at a low catalyst loading of 0.1 mol %. Furthermore, this catalytic system also proved to be highly effective in one-pot multiple couplings.**

Palladium-catalyzed coupling reactions, inspired by the 2010 Nobel Laureates' discoveries, are powerful and convenient one-step tools for the construction of carbon−carbon bonds.[1] The Suzuki coupling reaction of aryl halides with arylboronic acids represents one of the most synthetically valuable methods for the synthesis of biaryl derivatives.[2] Early studies on the coupling have performed predominantly with aryl iodides and bromides as substrates.[3] From a practical point of view, the use of aryl chlorides is typically more attractive due to their low cost and wide availability. However, the high C−Cl bond strength makes their activation difficult. The emergence of highly active catalysts provides new opportunities for the Suzuki coupling of these substrates. Especially, Pd catalysts derived from electron-rich, bulky di- or trialkylphosphanes[4] and *N*-heterocyclic carbenes[5] have led to considerable progress in this area. Most of the prominent catalysts display excellent reactivity for the coupling of deactivated aryl chlorides, while a relatively high catalyst loading and high temperature are often required to attain satisfactory results. There is still a need for more efficient catalysts which can significantly lower the catalyst loading and improve the reactivity with broad substrate generality. In this communication, we describe our discovery of a highly active palladium catalyst that facilitates the Suzuki reaction

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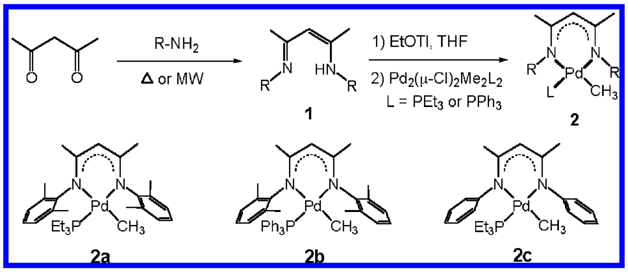
10.1021/ol102677r

of less reactive substrates under mild conditions and low catalyst loadings.

Transition metal β-diketiminates have gained much interest in the fields of metallo-organic chemical vapor deposition[6] and catalytic olefin polymerization.[7] However, they have received much less attention in other processes. A new class of air- and moisture-stable β-diketiminato-phosphane Pd complexes **2** could be easily prepared in three steps (Scheme 1). Acetylacetone reacted with primary amines under mild microwave irradiation to give β-diketimines **1** in high yields. Interestingly, this reaction could be complete within 30 min under solvent-free conditions. Deprotonation of **1** with EtOTl in THF followed by treatment with $Pd_2(\mu\text{-}Cl)_2Me_2L_2$ (L = PPh_3, PEt_3)[8] led to the formation of the corresponding Pd complexes **2**.

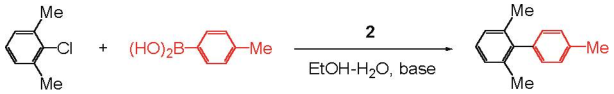
Scheme 1. Synthesis of β-Diketiminatophosphine Pd Catalysts **2**



A great deal of interest has recently been devoted to exploring the hindered Suzuki reaction due to the presence of di-*ortho*-substituted biaryls in numerous natural products, biologically active compounds, and valuable polymeric materials.[9] Despite considerable research effort, the coupling of hindered aryl chlorides with di-*ortho*-substitution has so far brought only limited success.[4a,f] Our main interest is concerned with activation of sterically hindered as well as electron-rich aryl chlorides under mild conditions.

Thus, we chose the coupling of 1-chloro-2,6-dimethylbenzene and *p*-tolyboronic acid as a model system for the optimization study (Table 1). The reaction was carried out in the presence of 0.1 mol % of **2a** and 2.0 equiv of K_2CO_3 as a base. We used aqueous ethanol as a reaction media for economic benefit, even though the activity was accelerated in other organic solvents (entries 1−3). To our delight, the coupling proceeded very well at 50 °C to give the product in excellent yield. A catalyst loading as low as 0.01 mol % was also shown to be effective, although a comparatively long reaction time was needed (entry 4). Moderate conversions were observed even at 40−25 °C (entries 5 and 6).

Table 1. Suzuki Coupling of 2-Chloro-1,3-dimethylbenzene with *p*-Tolylboronic Acid[a]



entry	**2** (mol %)	base	*t* (°C)	time (h)	yield (%)[e]
1	**2a**	K_2CO_3	50	8	91
2[b]	**2a**	K_2CO_3	50	6	95
3[c]	**2a**	K_2CO_3	50	6	90
4[d]	**2a**	K_2CO_3	50	24	70
5	**2a**	K_2CO_3	40	10	83
6	**2a**	K_2CO_3	25	24	60
7	**2a**	K_3PO_4	50	24	82
8	**2a**	Na_2CO_3	50	8	61
9	**2a**	Cs_2CO_3	50	8	53
10	**2a**	NaOMe	50	8	49
11	**2b**	K_2CO_3	50	8	53
12	**2c**	K_2CO_3	50	8	72

[a] General conditions: 2-chloro-1,3-dimethylbenzene (1.0 mmol), *p*-tolylboronic acid (1.2 mmol), **2** (0.1 mol %), base (2.0 mmol), EtOH−H_2O (2 mL, 1:1). [b] DMF-H_2O (2 mL, 1:1). [c] DMA-H_2O (2 mL, 1:1). [d] In the presence of 0.01 mol % of **2a**. [e] Isolated yield.

The use of K_3PO_4, Na_2CO_3, Cs_2CO_3, and NaOMe instead of K_2CO_3 gave inferior results under the same conditions (entries 7−10). It was noted that catalyst **2b** and **2c** led to an significant decrease in the rate (entries 11 and 12). This difference could be explained by the fact that the stronger electron-donating triethylphosphine ligand on the Pd metal lowers the activation energy for the oxidation step of the catalytic cycle more compared to triphenylphosphine. In addition, methyl groups on the phenyl rings also have a beneficial effect in enhancing the reactivity.

The Suzuki coupling of less reactive aryl chlorides was then investegated under the optimized reaction conditions (Figure 1). Deactivated aryl chlorides possessing electron-donating groups reacted with *p*-tolyboronic acid in the presence of 0.1 mol % of **2a** at 50 °C (**3a−d**). Noteworthy is that the catalyst system could promote the coupling of 2-chloroaniline bearing a free amino group (**3e**). Regardless of the substituent, all of the coupling reactions were carried out rapidly and efficiently to afford the desired biaryls in high yields. It was also observed that catalyst **2a** worked well for the coupling of more challenging di-*ortho*-substituted aryl chlorides while offering unprecedented reactivity and wide substrate scope under the mild conditions (**3f−k**). Additionally, hindered and electron-rich 4-chloro-3,5-dimethylphenol having a free hydroxy group was successfully combined with hindered 2,6-dimethylphenyl boronic acid to give a tetra-*ortho*-substituted biaryl (**3l**). To the best of our knowledge, catalyst **2a** shows the highest catalytic activity reported for the Suzuki coupling of sterically demanding aryl chlorides.

The Suzuki reaction has been used previously in the application of convenient diarylation of dibromobenzenes.[10] From the viewpoint of efficiency, a one-pot double coupling of inexpensive aryl dichlorides would be highly valuable for

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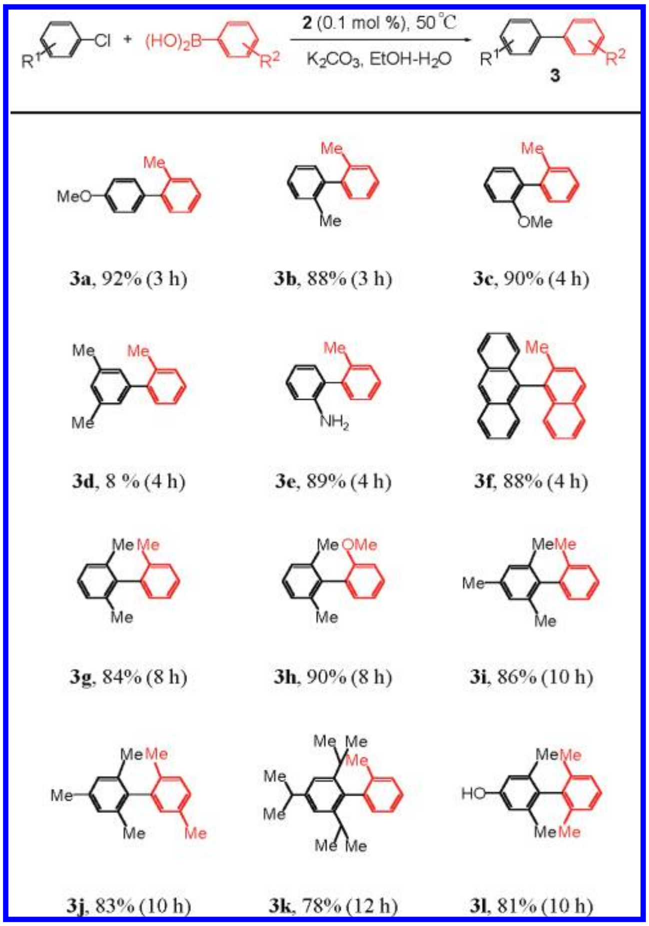

Figure 1. Suzuki coupling of aryl chlorides with arylboronic acids. Reaction conditions: Aryl chloride (1.0 mmol), arylboronic acid (1.3 mmol), **2a** (0.1 mol %), K_2CO_3 (2.0 mmol), EtOH−H_2O (2 mL, 1:1); Isolated yield.

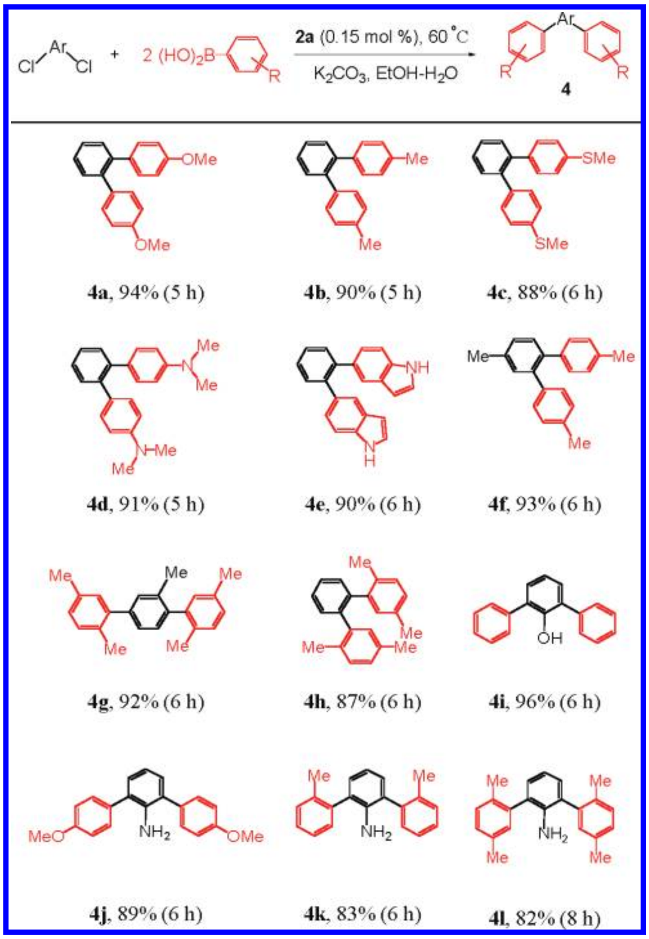

Figure 2. One-pot double Suzuki coupling of aryl dichlorides. Reaction conditions: Aryl dichloride (1.0 mmol), arylboronic acid (2.5 mmol), **2a** (0.15 mol %), K_2CO_3 (3.0 mmol), EtOH−H_2O (3 mL, 1:1); Isolated yield.

the synthesis of functionalized terphenyls. We proceeded to investigate the double coupling with 0.15 mol % of **2a** (Figure 2). An array of aryl dichlorides reacted with arylboronic acids in a single pot to give the dicoupled products in excellent yields (**4a−h**). In particular, we were able to dicouple highly deactivated aryl dichlorides having a strong electron-donating group such as a hydroxy and an amino group (**4i−l**). During the diarylation, the monocoupled adduct was scarcely formed. This catalytic system shows great practical potential for the facile synthesis of terphenyls via one-pot double couplings. To our knowledge, this is the first example of a challenging double Suzuki reaction of aryl dichlorides.

Polyarylbenzenes have attracted much attention in the field of organic optical and electronic devices.[11] A one-pot multiple Suzuki coupling leading to such polyarylbenzenes can be more challenging. It was possible to achieve a one-pot triple coupling at a catalyst level as low as 0.3 mol % Pd. 1,3,5-Triarylbenzenes were obtained exclusively in the coupling of 1,3,5-trichlorobenzene with different arylboronic acids at 60 °C (Figure 3).

We further extended this concept to a one-pot quadruple coupling (Figure 4). 1,2,4,5-Tetrachlorobenzene was coupled uneventfully with arylboronic acids in the presence of 0.5 mol % Pd. All chlorine atoms were replaced by aryl groups in high yields. Under these conditions, relatively hindered 2-chloro-1,3-dimethylbenzene was also found to be a capable coupling partner in this reaction. These transformations open up a one-step route to polyaryl-substituted aromatic compounds from readily available and inexpensive polychlorobenzenes.

All couplings of di-, tri-, and tetrachlorobenzenes with various arylboronic acids in the presence of low catalyst loadings of **2a** afford the corresponding products in high

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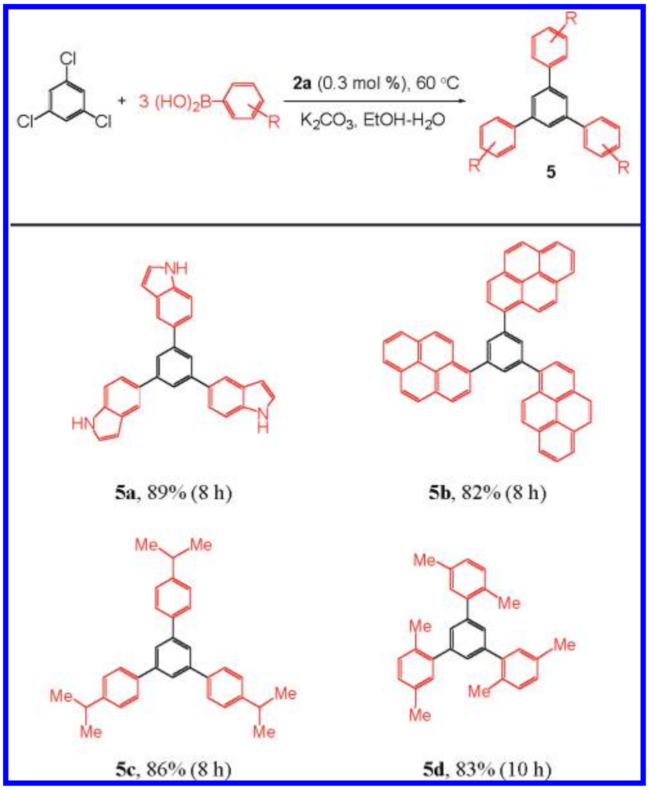

Figure 3. One-pot triple Suzuki coupling of 1,3,5-trichlorobenzene. Reaction conditions: 1,3,5-trichlorobenzene (1.0 mmol), arylboronic acid (3.9 mmol), **2a** (0.3 mol %), K_2CO_3 (5.0 mmol), EtOH−H_2O (4 mL, 1:1).

yields. This method would offer the attraction of reducing the number of steps required to access highly aryl-substituted arenes. These results represent a significant advancement in the Suzuki coupling reaction.

An interesting structural feature of **2a** concerns the presence of bulky diketimine and an electron-rich triethylphosphine ligand exerting a positive influence on the redox catalytic properties of palladium. However, it is unlikely that both of these ligands simultaneously coordinate on palladium through the catalytic cycle because the palladium complex is not able to undergo the coupling alone with the one remaining coordination site. It is envisaged that the catalytic system will facilitate the formation of a catalytically active monophosphine complex.[1c] Although the mechanism of the present coupling reaction is not yet obvious, the high activity is probably attributed to the enhanced nucleophilicity of the palladium species which promotes the cleavage of the inert Ar−Cl bond in the rate-limiting oxidation step.

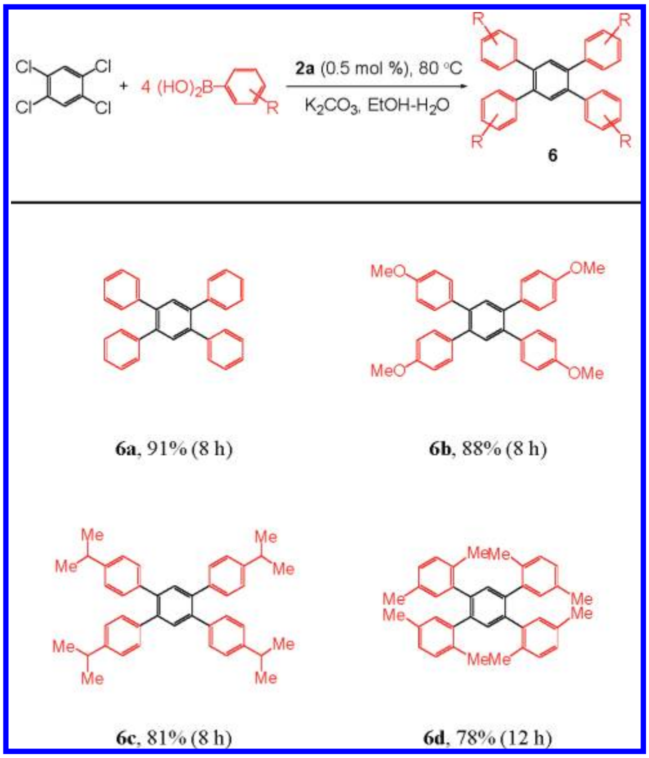

Figure 4. One-pot quadruple Suzuki coupling of 1,2,4,5-tetrachlorobenzene. Reaction conditions: 1,2,4,5-tetrachlorobenzene (1.0 mmol), arylboronic acid (5.2 mmol), **2a** (0.5 mol %), K_2CO_3 (6.0 mmol), EtOH−H_2O (5 mL, 1:1).

In conclusion, we have developed a highly active and general catalyst system for the Suzuki reactions of deactivated or hindered aryl chlorides. Under these conditions, efficient one-pot multiple Suzuki couplings were realized. We anticipate that the application of this catalyst can be extended to other catalytic processes.

Acknowledgment. This work was supported by a National Research Foundation of Korea grant funded by the Korean Government (2009-0072013).

Supporting Information Available: General experimental procedures, synthesis characterization details, and copies of ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102677R